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10/520,008	12/30/2004	Chunyu Cao	CAO1	9498

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,008	CAO ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-10 and 17-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10, 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on *02/18/2009* in response to office action mailed on 11/25/2008 has been acknowledged.

Claims 17 and 18 are amended.

Claims 1, 2 and 11-16 were previously canceled.

Claims 3-10, 17-27 *are pending and are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 3-10, 17-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reason of record set forth in the office action of 02/22/2008 and reiterated in the office action mailed on 11/25/2008. .

Response to Applicant's arguments of *02/18/2009:*

The Applicant amends claims partially with respect to rejected issue and indicates that amendment should overcome the rejection.

The applicants arguments and amendments are fully considered however, they are found not persuasive because (1) Specification does not contain embodiments that teach to exclude other sequences associated with in the mutagenic inverted repeat nucleic acid sequences (DNA of the invention). (2) All the examples provided include other associated sequences as structural elements and therefore there was as such no contemplation that the invention was meant to be to the exclusion of other sequences. (3) Original claims have a "comprising language" and as such necessarily does not demonstrate or convey that the invention is to exclude all other sequences. Applicant's current amendments to reintroduce the recitation "having" instead of the rejected language "consisting of" to only to one part of the claim will not do. The Applicant is required to re introduce the "comprising" language as used before for the inverted repeat too to overcome the rejection because an Artisan would not have understood the invention to be to the exclusion of other sequences. Hence the rejection is maintained.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 23-27 stand rejected under 102(b) as being anticipated by Ohshima et al (US Patent Number: 5643762; art of record).

The Claims are drawn to a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target

nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence wherein said inverted DNA repeat insert was prepared excised from a plasmid using restriction enzymes or amplified from the plasmid using PCR and 2) transferring the DNA having an inverted repeat sequence into a cell. The method is further limited wherein the target is in the cytoplasm or in the nucleus and wherein a plurality of mutations are simultaneously introduced into the target nucleic acid wherein the mutation is a substitution, deletion, and/or insertion of a nucleotide.

Regarding claims Ohshima teaches a method of introducing a mutation into a nucleotide sequence of a target nucleic acid (selected gene) comprising preparing a sL DNA that comprises a sense strand sequence and antisense strand of target nucliec acid containing a mutation and the sense strand and antisense strand sequence are arranged in tandem (entire article; abstract; Fig.1; Fig.7) and wherein the mutation to be introduced is located on the sense and antisense stand (Fig.7; co.13-16; col.17, lines 6-20) and Ohshima further teaches a method of preparing said inverted repeat single stranded mutagenic DNA that can form stem loop structure and method of introducing mutations (col.2, lines 9-47; col.17, lines 6-20). With regard to newly introduced limitation the Applicant should note that introducing a restriction site or using restriction enzymes to precisely cut out the portion of a double stranded DNA needed (for example the inverted repeat of the invention) or using PCR or synthetic methods to obtain precisely the required sequences in a template DNA has become inherent to the relevant art (molecular biology) at he time of instant invention. In fact Oshima does teach using restriction enzyme sites and restriction of the DNA in and around the inverted repeat (e.g., see Fig 1 A &B). Ohshima thus clearly anticipates the invention as instantly claimed

Further, and alternatively, it would have been obvious to one of the skill in the art to remove the irrelevant portions of the molecule for example the 3'overhanging sequences in the folded single strand inverted repeat structure of sLDNA shown in Fig.4 of Oshima reference and use it for introducing a desired mutation into a cellular gene by

homologous recombination. The artisan would do so as the irrelevant portions have no function, and hence their removal would still yield an active molecule of the same function. Moreover, the artisan would have reasonable expectation of success as the same functions of the molecule are provided and nothing in the art would lead the artisan to believe it would not work. Thus the invention as claimed is obvious.

Response to Applicant's arguments of *02/18/2009:*

The Applicant amends claims and introduces new limitation of using restriction enzyme or PCR technology to obtain precisely the inverted repeat sequence. The Applicant further argues that such an amendment to overcome the anticipation rejection based on Oshima reference.

The Applicants arguments are however found not persuasive because such a step of generating a DNA fragment including precisely the sequences needed either using an enzyme based restriction technology or using polymerase chain reaction (PCR) technology or using synthetic technology for relatively short fragments have become so ingrained or have become so a part and parcel of the molecular biology technology at the time of instant invention so as to an artisan make the "inherency" call. Further Oshima does teach using restriction enzyme sites and restriction of the DNA in and around the inverted repeat of the invention (e.g., see Fig 1 A &B). Ohshima thus clearly anticipates the invention as instantly claimed. Moreover, the artisan would have reasonable expectation of success of obtaining precisely the required DNA fragment using above mentioned technologies and nothing in the art would lead the artisan to believe it would not work. Thus the invention as claimed is also clearly obvious. Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-10, 17-27 stand rejected under 35 USC 103 (a) as being unpatentable over Ohshima et al (US Patent Number: 5643762; art of record) in view of in view of Wengel et al (WO 99/14226; art of record), Dean et al (US Patent No: 6,130,207; art of record) and Bissler et al (1998, Frontiers in Biosciences 3:d408-418; art of record).

The Claims are drawn to a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence wherein said inverted DNA repeat insert was prepared excised from a plasmid using restriction enzymes or amplified from the plasmid using PCR and 2) transferring the DNA having an inverted repeat sequence into a cell. The method is further limited wherein the target is in the cytoplasm or in the nucleus and wherein a plurality of mutations are simultaneously introduced into the target nucleic acid wherein the mutation is a substitution, deletion, and/or insertion of a nucleotide.

Regarding claims Ohshima teaches a method of introducing a mutation into a nucleotide sequence of a target nucleic acid (selected gene) comprising preparing a sL DNA that comprises a sense strand sequence and antisense strand of target nucliec acid containing a mutation and the sense strand and antisense strand sequence are arranged in tandem (entire article; abstract; Fig.1; Fig.7) and wherein the mutation to be introduced is located on the sense and antisense stand (Fig.7; co.13-16; col.17, lines 6-20) and Ohshima further teaches a method of preparing said inverted repeat single stranded mutagenic DNA that can form stem loop structure and method of introducing mutations (col.2, lines 9-47; col.17, lines 6-20). Further it would have been obvious to one of the skill in the art to use single or double stranded nucleic acid consisting only of the elements in said mutagenic inverted repeat nucleic acid as instantly claimed. Ohshima

however, does not teach using modified bases or LNAs in the invention and further does not teach a binding motif sequence for a protein having a nuclear transport signal.

Wengel discloses the use of LNAs of his invention improve the "affinity and specificity towards complementary RNA and DNA oligomers" (see abstract). Wengel teaches that his LNAs are useful for preparing oligomers (page 37). Wengel teaches that the LNAs of his invention have surprisingly good hybridization properties with a substantially higher 3'exonucleolytic stability than unmodified oligonucleotides (page 46-48). Wengel further teaches that his LNAs are useful in modifying gene expression via antisense and therapeutic strategies (see abstract and introduction).

Dean teaches a plasmid comprising a DNA binding sequence specific for transcription factors (column 2, lines 54-67). Dean teaches that the binding sites allow transcription factors to bind to the plasmid and import the plasmid into the nucleus, thereby allowing the DNA to utilize the transcription factor nuclear localization signal for nuclear import (column 2, lines 54-67). Dean teaches that the binding sites can be for transcription factors such as AP1, Ap4, and Sp1 (column 3, lines 3-8). Dean teaches that the DNA to be imported into the nucleus can be flanked by IR sequences (column 8, lines 31-50). Dean teaches the DNA insert integrates into the host genome through homologous recombination at homologous sequences (column 11, lines 2—24). Dean further teaches that two problems hindering gene therapy are, "(1) gene transfers to non-diving cells are still extremely inefficient and (2) gene transfer to specific desired non-dividing cells within a population of other cell types is even more inefficient. Thus any way to increase the amount of gene transfer will greatly benefit this emerging field" (column 1, lines 18-22) and in order to fully exploit the potential for gene therapy, there is a "continuing need for ways to increase the amount of gene transfer to cells" (column 1, lines 64-67). Dean teaches that his invention, a plasmid comprising a cell-specific nuclear targeting molecule comprising a transcription factor binding motif meets this need (column 2, lines 5-27).

Bissler teaches regarding the nature of the inverted repeats in the eukaryotic genome and the well known art observation that inverted repeats tend to engage in intra and intermolecular base pairing by their ability to adopt hairpin and cruciform structures

that can introduce frame shift mutations and the imperfect repeats can introduce additional mutations carried in them (entire article; abstract).

Thus it would have been obvious for one of ordinary skill in the art to incorporate into Ohshima,s method of mutagenesis using inverted repeats consisting of sense strand and antisense strand sequence of a target nucleic acid a step of including modified bases to stabilize the inverted repeat sequence as taught by Wengel and further use a sequence that bind a nuclear localization factor as taught by Dean and use the inverted repeat sequences to introduce multiple mutations including a nucleotide substitution, deletion and or insertion into the target gene as observed by Bissler. One of skill in the art would have been motivated to use the method of introducing mutations using targeted inverted repeat sequences as it amply increases the efficiency of inducing mutations into the gene. One of ordinary skill in the art would have reasonable expectation of success making using an inverted repeat sequence for mutagenesis of the DNA in a cell because the art teaches that it is routine to make nucleic acid with inverted repeat sequence containing desired mutation and further stabilizing a nucleic acid cells by having certain modified nucleotides, introducing the inverted sequence into a cell, nuclear targeting, and the nature of interaction of inverted repeats in human genome. Thus, the claimed invention was *prima facie* obvious.

Response to Applicant's arguments of *02/18/2009:*

The Applicant amends claims and introduces new limitation of using restriction enzyme or PCR technology to obtain precisely the inverted repeat sequence. The Applicant further argues that such an amendment to overcome the obviousness rejection based on Oshima reference. The Applicant further argues that each of the supporting references used in obviousness rejection namely Wengel, Dean and Bissler references do not teach the whole invention including "excising an inverted repeat DNA insert in which……template" (p.9 of the response).

The Applicants arguments are however found not persuasive because such a step of generating a DNA fragment including precisely the sequences needed either using an

enzyme based restriction technology or using polymerase chain reaction (PCR) technology or using synthetic technology for relatively short fragments have become so ingrained or have become so a part and parcel of the molecular biology technology at the time of instant invention so as to an artisan make the "inherency" call. Further Oshima does teach using restriction enzyme sites and restriction of the DNA in and around the inverted repeat of the invention (e.g., see Fig 1 A &B). Ohshima thus clearly anticipates the invention as instantly claimed. Moreover, the artisan would have reasonable expectation of success of obtaining precisely the required DNA fragment using above mentioned technologies and nothing in the art would lead the artisan to believe it would not work. The Applicant arguments regarding the supporting references not teaching the whole invention as recited above was found not persuasive. The Applicant should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). Following the above principle, the combination of Oshima, Wengel, Dean and Bissler references clearly teach all the limitations of the instant invention. Hence the invention as claimed is clearly obvious to one of skill in the art at the time of the Applicants instant invention. Hence the rejection is maintained.

Conclusion:

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.*, whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/

Primary Examiner, Art Unit 1633